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Prevalence and Contribution of BRCA1 Mutations in Breast Cancer and Ovarian Cancer: Results from Three U.S. Population-Based Case-Control Studies of Ovarian Cancer

Alice S. Whittemore, Gail Gong, and Jacqueline Itnyre

Department of Health Research and Policy, Stanford University School of Medicine, Stanford.

Summary

We investigate the familial risks of cancers of the breast and ovary, using data pooled from three population-based case-control studies of ovarian cancer that were conducted in the United States. We base estimates of the frequency of mutations of BRCA1 (and possibly other genes) on the reported occurrence of breast cancer and ovarian cancer in the mothers and sisters of 922 women with incident ovarian cancer (cases) and in 922 women with no history of ovarian cancer (controls). Segregation analysis and goodness-of-fit testing of genetic models suggest that rare mutations (frequency .0014; 95% confidence interval .0002–.011) account for all the observed aggregation of breast cancer and ovarian cancer in these families. The estimated risk of breast cancer by age 80 years is 73.5% in mutation carriers and 6.8% in noncarriers. The corresponding estimates for ovarian cancer are 27.8% in carriers and 1.8% in noncarriers. For cancer risk in carriers, these estimates are lower than those obtained from families selected for high cancer prevalence. The estimated proportion of all U.S. cancer diagnoses, by age 80 years, that are due to germ-line BRCA1 mutations is 3.0% for breast cancer and 4.4% for ovarian cancer. Aggregation of breast cancer and ovarian cancer was less evident in the families of 169 cases with borderline ovarian cancers than in the families of cases with invasive cancers. Familial aggregation did not differ by the ethnicity of the probands, although the number of non-White and Hispanic cases ($N = 99$) was sparse.

Introduction

The past decade has seen the identification of several genes that increase susceptibility to site-specific cancers. These advances have generated considerable controversy about the advisability of clinical testing for germ-line mutations of the relevant genes. In light of this controversy and of the intensity of public interest in the issue, it is important that clinicians, public-health workers, and patients have information on the prevalence of specific germ-line mutations in the general population, the age-specific cancer risks associated with having such mutations, and the proportion of site-specific cancer attributable to the mutations.

Breast cancer and ovarian cancer risks associated with mutations of BRCA1 have been estimated by examining the risks of contralateral breast cancer and of ovarian cancer among women with breast cancer in families linked to BRCA1 (Easton et al. 1995). However, because these families were selected for multiple occurrences of breast cancer and ovarian cancer, their cancer experience may not be representative of cancer risks in the general population. Here we pool reported familial cancer data from three U.S. population-based case-control studies of ovarian cancer to estimate mutation prevalence and penetrance in the general population. BRCA1 mutations have been estimated to account for 88% (95% confidence interval [CI] range 74%–97%) of families containing multiple cases of both breast cancer and ovarian cancer and no cases of male breast cancer (Narod et al. 1995). Because of the ovarian cancer case-control design of the studies analyzed here, most of the 129 families with two or more cases of breast cancer or ovarian cancer contain at least one woman with each of the two malignancies. Thus, it is likely that most of these families are segregating mutations of BRCA1. We estimate the prevalence of germ-line mutation carriers in the U.S. population, the age-specific risks of breast cancer and ovarian cancer in mutation carriers, and the proportions of all breast cancers and ovarian cancers associated with these mutations.

Subjects and Methods

Study Populations

The first of the three studies, the Cancer and Steroid Hormone (CASH) Study (CASH 1987), included 554 incident cases of histologically confirmed epithelial ovarian cancer (340 invasive cancers, 121 borderline cancers,

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Address for correspondence and reprints: Dr. Alice S. Whittemore, Department of Health Research and Policy, Redwood Building, Room T204, Stanford University School of Medicine, Stanford, CA 94305-5092

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and 93 cancers of unknown malignant potential), diagnosed at ages 20–54 years in the period 1980–82. These cases were ascertained from eight population-based cancer registries included in the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute. One group of control women was selected for comparison with ovarian cancer cases and with breast cancer and endometrial cancer cases enrolled in the study. These women were selected, by use of random-digit dialing, from the same geographic regions as the cancer cases and were chosen so that their age distribution (within 5-year intervals) equaled that of the breast cancer cases.

The second study (Casagrande et al. 1979) included 141 histologically confirmed cases of incident invasive epithelial ovarian cancer, diagnosed at ages 25–49 years in Los Angeles County during the period 1973–76. Control women were matched individually to cases on the basis of age and race (White, Black, Asian, or other) and were selected from the same neighborhoods as the cases. Cases ($N = 6$) and controls ($N = 8$) with any prior cancer were excluded.

The third study (Whittemore et al. 1988) included 227 women with incident epithelial ovarian cancer (170 invasive cancers, 48 borderline cancers, and 9 cancers of unknown malignant potential), diagnosed at ages 20–85 years in the San Francisco Bay area during the period 1983–86. Two sets of control women were selected. The first set consisted of women selected by use of random-digit dialing. The second set consisted of women from the same hospitals as the cases. Each set of controls was matched to the cases on the basis of race (White, Black, Asian, or other) and was selected so that its age distribution (within categories of race and within 5-year intervals) equaled that of the cases.

In each of the three studies, a woman was excluded as a control if she had a prior history of ovarian cancer, if both ovaries had been removed, or if she did not know whether both ovaries had been removed. Further details concerning protocols and response rates of the three studies can be found in the original reports (Casagrande et al. 1979; CASH 1987; Whittemore et al. 1988).

In summary, the three studies included 922 cases with epithelial ovarian cancer, classified as invasive ($N = 651$), borderline ($N = 169$), or of unknown malignant potential ($N = 102$). Of these cases, 823 were White non-Hispanic, 40 were Black, 35 were Hispanic, and 24 were of Asian or other ethnicity. The combined studies also included 5,108 control women. We excluded from analysis a case or a control if she did not know her number of sisters, if she knew the breast/ovarian cancer status of none of her sisters, or if she had no sisters and her mother's breast cancer status and ovarian cancer status were unknown. These exclusions applied to none of the cases and to 157 (3.1%) of the controls, leaving 4,951 eligible controls (4,229 White non-Hispanic, 424 Black, 166 Hispanic, and 132 Asian or other ethnicity). To reduce computing time for the segregation analysis, we included only a random subsample containing 922 of these controls. Thus, the final analysis included 922 cases and 922 controls (hereafter called "probands").

Each proband reported the vital status of her mother and her sisters and their ages at death or at the time of interview. She also reported any occurrences of breast cancer or ovarian cancer in these relatives or of breast cancer in herself. If the proband reported such a cancer, she also reported the age when the cancer was diagnosed. Such information was gathered on both full sisters and half sisters, without distinguishing between the two. Information on male breast cancer was not collected.

Analysis

A detailed description of data processing for the probands can be found in a report by Whittemore et al. (1992). For this analysis, if the cancer status of a proband's relative was unknown or if the relative was reported to have had cancer at an unknown site, she was assumed not to have had breast cancer or ovarian cancer. If a relative's age at cancer diagnosis was unknown, it was estimated by determining the mean age of the cancer in all affected relatives, specific for the type of relative (mother vs. sister), the cancer site (breast vs. ovary), and the proband's case-control status. Such incomplete data occurred in the families of 39 of the cases and 34 of the controls included in the present analysis.

Model fitting.—Each family member was assumed to be either a carrier or a noncarrier of a germ-line mutation. Conditional on her carrier status, a woman was assumed to develop breast cancer and/or ovarian cancer according to the multistate probability model shown in figure 1. She was assumed to remain in the disease-free state until age 15 years. Thereafter, she was at risk of developing cancer or of being censored by death or by study termination at age- and carrier-specific hazard rates. Given the occurrence of either breast cancer or ovarian cancer, she was at risk of developing the other cancer at the same age- and carrier-specific rate or of being censored at rates that depended on her then current cancer state. Given their genotypes, family members' times to onset of cancer were assumed to be mutually independent. Given a woman's carrier status, her times to onset of breast cancer and ovarian cancer were assumed to be independent of each other and of her time to censoring. Further details of this multistate probability model are described in a study by G. Gong and A. S. Whittemore (unpublished data).

We fit three hazard-rate models to the data. For all three models, different families were assumed to contribute independent data. The first model, designated the "nongenetic model," assumes that a woman's age-specific hazard rates for both cancers are independent of

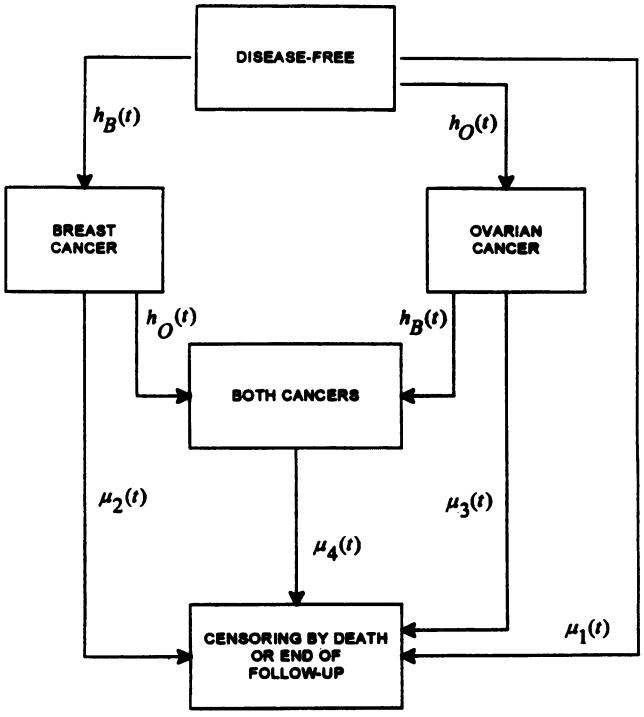

Figure 1 Multistate probability model for the occurrence of breast cancer and ovarian cancer in carriers and noncarriers. All women remain in the disease-free state until age 15 years. Thereafter, a woman of age $t > 15$ years is at risk of developing cancer of the breast or ovary, at the carrier-specific hazard rates of $h_B(t)$ and $h_O(t)$, respectively. She also may be censored by death or study termination at the rate of $\mu_1(t)$. Given the occurrence of either breast cancer or ovarian cancer, a woman is at risk of developing the other cancer at the same rates, $h_B(t)$ and $h_O(t)$, or of being censored at the rates of $\mu_2(t)$ and $\mu_3(t)$, respectively. Given their genotypes, family members' times to cancer onset are assumed to be mutually independent.

her carrier status. Thus, times to cancer in relatives are mutually independent. The breast cancer hazard rate was assumed to be a constant h_{B1} at ages 15–39 years, a constant h_{B2} at ages 40–59 years, and a constant h_{B3} at ages $\geq$60 years. The ovarian cancer hazard rate was modeled similarly, with constant values h_{O1}, h_{O2}, and h_{O3}, in the same three age intervals, respectively. The nongenetic model thus depends on the six parameters h_{B1}, h_{B2}, h_{B3}, h_{O1}, h_{O2}, and h_{O3}.

The second model, designated the "general dominant model," specifies that the age-specific hazard rates for breast cancer and ovarian cancer depend on carrier status. Each of the two carrier-specific hazard rates for each of the two cancer types was assumed to be constant within each of the age intervals described above. The probability that one or both of the proband's parents carried a mutation was determined by Hardy-Weinberg equilibrium, with an unknown mutation frequency (q). The distribution of carriers among the proband and her sisters was determined by dominant Mendelian inheritance. The general dominant model depends on 13 parameters: q and the three hazard-rate constants for each of the two diseases, for both carriers and noncarriers.

The third model is a submodel of the general dominant model, obtained by assuming that the ovarian cancer hazard rate in carriers is proportional to that of noncarriers, with proportionality constant C_O. This model, which we call the "proportional ovary model," specifies that the hazard-rate ratio in carriers relative to noncarriers is independent of age. Testing this model is of interest, because it provides information on the age distribution of ovarian cancer in mutation carriers, relative to that of the general population. The proportional ovary model involves the following 11 parameters: q, the three breast cancer hazard-rate constants for carriers and the three for noncarriers, the three ovarian cancer hazard-rate constants for noncarriers, and the proportionality constant C_O.

Parameters in the nongenetic model were estimated by maximizing the likelihood of the independent censored times to breast cancer and ovarian cancer in the probands' mothers and sisters and of the censored times to breast cancer in the probands in the CASH and Whittemore studies, by use of standard Poisson regression methods (Kelsey et al. 1996). Parameters in the general dominant model and the proportional ovary model were estimated by maximizing the likelihood of all the family members' times to breast and/or ovarian cancer, conditional on the proband's ovarian cancer status and on her age at diagnosis (case) or interview (control). For families in the Casagrande study, the likelihood also was conditional on the proband's having survived breast cancer until her age at ovarian cancer diagnosis (case) or interview (control). The data contained insufficient numbers of older women with breast cancer to provide a stable estimate for the breast cancer hazard rate among mutation carriers of age $\geq$60 years. Therefore, we set this parameter at the value of .01681, which was obtained by Claus et al. (1991) in their segregation analysis of population-based case-control breast cancer data.

For all models, we estimated the variances of parameter estimates by inverting the likelihood-based observed-information matrix. We constructed nonsimultaneous 95% CIs by transforming each parameter so that its range was the entire real line, by assuming that the transformed estimate was Gaussian, and then by converting the upper and lower Gaussian confidence limits back to the original scale. (For example, since q lies in the unit interval, we assumed a Gaussian distribution for $\log[q/(1-q)]$, which can take on all real values. Similarly, since the age- and carrier-specific incidence rates are nonnegative, we assumed a Gaussian distribution for their logarithms, which can take on all real values.)

Goodness-of-fit.—Since the proportional ovary model is nested in the general dominant model, we used the likelihood-ratio statistic to evaluate its goodness-of-fit. However, likelihood-ratio statistics cannot provide good-

Table 1

Distribution of Ovarian Cancer Case and Control Probands, by Number of Sisters, and Reported Prevalence of Breast Cancer and Ovarian Cancer in Their First-Degree Relatives

No. of Sisters	Probands		No. of Affected Mothers		No. of Affected Sisters	
	N	No. Affected with Breast Cancer	Breast Cancer	Ovarian Cancer	Breast Cancer	Ovarian Cancer
			Case Families			
0	259	5	20	6	...	...
1	274	4	16	10	13	0
2	188	5	11	4	8	0
3	98	1	4	1	4	3
4	53	0	0	1	4	1
5	27	0	3	0	1	1
6+	23	0	1	0	1	1
Total	922	15	55	22	31	6
			Control Families			
0	261	4	18	1	...	...
1	277	8	10	2	4	1
2	183	1	7	1	6	1
3	104	3	2	1	8	0
4	43	0	3	0	0	0
5	30	0	1	0	1	0
6+	24	0	1	0	0	0
Total	922	16	42	5	19	2

ness-of-fit tests for either the nongenetic model or the general dominant model. Therefore, we evaluated these two models by comparing the observed numbers of pairs of affected relatives with the numbers predicted by the model. To do so, we computed an efficient score statistic of the form $S = (O - E)/\mathrm{SE}$ and referred it to a table of critical values for a standard Gaussian distribution (A. S. Whittemore, J. Halpern, and G. Gong, unpublished data). Here O and E represent the observed and predicted numbers of affected relative pairs, respectively, for which a woman was considered "affected" if she had developed the given cancer (ovary or breast) by a specified age, and SE represents the standard error of 0.

Results

Column 2 of table 1 shows the distributions of case and control probands according to their numbers of sisters. Column 3 shows the number of probands who reported a prior diagnosis of breast cancer. Columns 4–7 give the numbers of affected mothers and sisters of probands, by sibship size. In row 4, for example, 98 ovarian cancer cases reported having three sisters. Of these, 1 ovarian cancer case reported having a prior breast cancer, 4 reported having a mother with breast cancer, and 1 reported having a mother with ovarian cancer. In addition, four sisters of the 98 probands were reported to have had a diagnosis of breast cancer, and three sisters were reported to have had a diagnosis of ovarian cancer.

Table 2 shows the numbers of affected mother/daughter and sister/sister pairs, according to type of cancer (breast vs. ovary). The small number of affected sister/sister pairs ($N = 41$) relative to the number of mother/

Table 2

Number of Pairs of Relatives with Breast Cancer or Ovarian Cancer, by Ovarian Cancer Status of the Proband

Cancer Type	Mother-Daughter	Sister-Sister	Total
	Case Families		
Breast/breast	7	5	12
Breast/ovarian	57	30	87
Ovarian/ovarian	22	6	28
Total	86	41	127
	Control Families		
Breast/breast	3	2	5
Breast/ovarian	1	1	2
Ovarian/ovarian	0	0	0
Total	4	3	7

NOTE.—Data include pairs of relatives in which one member is the proband.

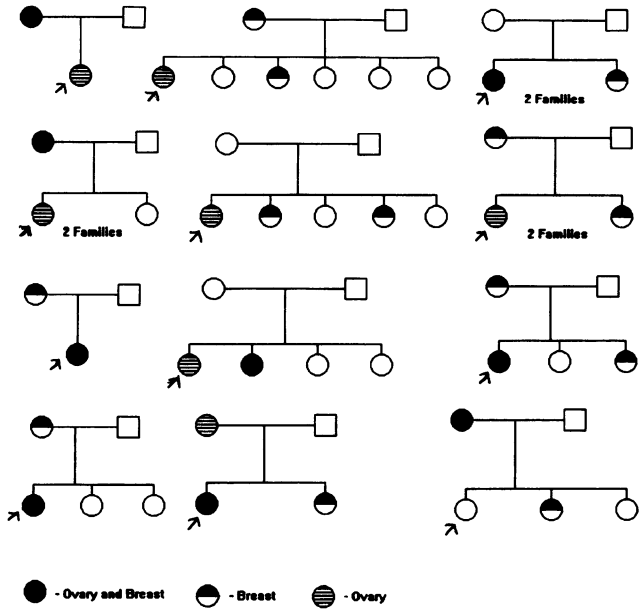

Figure 2 Pedigrees of 14 ovarian cancer cases and 1 control, who reported three or more breast cancer or ovarian cancer diagnoses in themselves, their mothers, or their sisters. Completely blackened circles represent cases with both breast cancer and ovarian cancer. The arrows indicate the probands.

daughter pairs ($N = 86$) reflects the age distributions of the probands and their sisters; by design, most probands were <55 years of age at the time of interview.

Fourteen ovarian cancer cases and one control reported the diagnosis of three or more breast cancers and/or ovarian cancers in themselves, their mothers, or their sisters. As seen in figure 2, 3 of the 14 cases reported a diagnosis of both breast cancer and ovarian cancer in their mothers. Six cases reported a prior breast cancer in themselves and a breast cancer or ovarian cancer in either their mothers or their sisters (or both). Three cases reported a mother and a sister with breast cancer, one case reported two sisters with breast cancer, and one case reported a sister with both breast cancer and ovarian cancer.

The likelihood-ratio test rejected the proportional ovary model ($\chi^2_2 = 5.2$, $P = .08$) relative to the general dominant model. The statistics shown in table 3 indicate that the nongenetic model also fit poorly. As seen in table 3, this model significantly underpredicted the numbers of affected mother/daughter and sister/sister pairs. In contrast, there were no statistically significant differences between observed numbers of affected pairs and those predicted by the general dominant model. Six cases and no controls reported having two or more first-degree relatives with breast cancer or ovarian cancer or both. The expected number of such cases under the general dominant model was 10.4, a nonsignificant difference ($\chi^2_1 = 1.8$, $P = .17$).

We also evaluated how well the nongenetic model and the general dominant model fit the breast cancer data and ovarian cancer data in the families of the cases with borderline ovarian cancers ($N = 169$) and in the families of the non-White or Hispanic probands (99 cases and 137 controls). The family data for the borderline ovarian cancer cases were too sparse to distinguish these two models, although there were some suggestive discrepancies between the data and both models. Specifically, there were more mother/daughter pairs with breast cancer and ovarian cancer by age 75 years than were predicted by the nongenetic model ($P < .001$). In contrast, the general dominant model overpredicted the number of affected relative pairs in 15 of the 18 relative-pair comparisons listed in table 3, although none of these differences was statistically significant. The families of non-White and Hispanic probands contained significantly more pairs of young (<50 years) relatives with breast cancer and more pairs of young relatives with breast cancer and ovarian cancer than were predicted by either model. No other statistically significant differences were seen.

The frequency of mutations, as estimated from the general dominant model, was $q = .0014$ (95% CI .0002–.011). This estimate corresponds to a prevalence of one germ-line mutation carrier in 345 individuals in the general U.S. population. As seen in table 4, the estimate is roughly twice the value $q = .0006$ (95% CI .0002–.001), which was obtained by Ford et al. (1995) on the basis of breast cancer and ovarian cancer mortality, in England and Wales, among relatives of women with breast cancer and ovarian cancer (hereafter called "the British data"). Both these estimates are lower than the value $q = .0033$ obtained from segregation analysis of data from a U.S. population-based case-control breast cancer study (Claus et al. 1991).

Table 5 gives the estimated cumulative cancer risks among mutation carriers and noncarriers. Among carriers, the overall risks by ages 70 and 80 years are 68.6% and 73.5%, respectively, for breast cancer and 21.5% and 27.8%, respectively, for ovarian cancer. The corresponding estimates for noncarriers are 4.5% and 6.8% for breast cancer and 1.1% and 1.8% for ovarian cancer. As seen in Table 5, the cancer-risk ratio in carriers as compared with noncarriers decreases sharply with age at onset for both breast cancer and ovarian cancer. The estimates of breast cancer risk among mutation carriers are similar to those obtained from the population-based case-control breast cancer study analyzed by Claus et al. (1991).

Figure 3 shows that both sets of estimated breast cancer risks are lower than those obtained by analysis of cancer occurrence in women from families linked to BRCA1 (Easton et al. 1995). Similarly, the estimates of ovarian cancer risk among mutation carriers in table 5 are lower than those obtained from the BRCA1-linked families (fig. 3). This figure also shows that a carrier's

Table 3

Difference ($O - E$) Between Observed and Expected Pairs of Relatives with Breast Cancer or Ovarian Cancer

	$O - E$, by Model and Cancer Type					
	Nongenetic Model			General Dominant Model		
Pair	Breast/Breast	Breast/Ovarian	Ovarian/Ovarian	Breast/Breast	Breast/Ovarian	Ovarian/Ovarian
	Both Women Diagnosed at Age <50 Years					
Mother-daughter	4.9**	6.4	3.4*	.8	−2.0	1.0
Sister-sister	3.8**	6.7*	.2	−.2	2.7	−1.1
Total	8.7**	13.1**	3.6	.6	.7	−.1
	Both Women Diagnosed at Age <75 Years					
Mother-daughter	2.9	4.8	9.7**	−1.7	−4.8	6.4
Sister-sister	1.9	4.4	.3	−4.9	−3.9	−1.9
Total	4.8	9.2	10.0**	−6.6	−8.7	4.5

*$P < .05$.
**$P < .001$.

risk for either breast cancer or ovarian cancer by age 70 years is estimated at only 75%, which is in contrast to the estimated 93%–95% risk obtained from the families linked to BRCA1.

Table 6 shows the estimated proportions of germ-line mutation carriers among all U.S. women with breast cancer and ovarian cancer, by age at diagnosis. Overall, only 3.0% of all breast cancer cases and 4.4% of ovarian cancer cases are associated with these mutations. As seen in table 6, the present estimates are somewhat larger than those obtained from the British data. The two sets of data suggest that 5%–10% of all breast cancers diagnosed among women <40 years of age occur in carriers of germ-line mutations.

Discussion

We have pooled family breast cancer data and ovarian cancer data from three population-based case-control studies of ovarian cancer to estimate the frequency and penetrances of mutations conferring increased risk of these neoplasms. While we cannot distinguish the specific genes involved, other evidence suggests that most of the high-risk families identified by the three studies are segregating mutations of BRCA1. We have used the pooled data to estimate the combined frequency of mutations, the age-specific cumulative risks of breast cancer and ovarian cancer that are associated with the mutations, and the fraction of all breast cancer cases and ovarian cancer cases who carry germ-line mutations.

This study provides further evidence that the frequency of BRCA1-mutation carriers in the general population is low. The present estimate that 1/345 individuals carries a mutation is intermediate between the value 1/833, obtained from the British data (Ford et al. 1995), and the value 1/151, obtained from U.S. population-based case-control breast cancer data (Claus et al. 1991).

Table 4

Prevalence of BRCA1/BRCA2 Mutations, from Population-Based Studies

Estimated q (95% CI)	Estimated Carrier Prevalence in Population (95% CI)	Population	Reference
.0014 (.0002–.011)	$\frac{1}{345}\left(\frac{1}{2{,}596}-\frac{1}{46}\right)$	Families of U.S ovarian cancer cases and controls	Present study
.0006 (.0002–.001)	$\frac{1}{833}\left(\frac{1}{2{,}500}-\frac{1}{500}\right)$	Families of women with incident breast cancer or ovarian cancer, in England and Wales	Ford et al. (1995)
.0033 (. . .)	$\frac{1}{152}(\ldots)$	Families of U.S. breast cancer cases and controls	Claus et al. (1991)

The 95% CI for the present estimate includes both these values. The designs of this study and that of Ford et al. (1995) have yielded high-risk families who largely contain both breast cancer and ovarian cancer and so are likely to be segregating mutations of BRCA1. In contrast, most of the high-risk families in the analysis by Claus et al. (1991) contain multiple cases of breast cancer with few cases of ovarian cancer and so are apt to be segregating BRCA1, BRCA2, and possibly other breast cancer–susceptibility genes. Thus the higher estimate q = .0033 reported by Claus et al. (1991) may reflect the combined prevalence of mutations in both genes, and the corresponding penetrance estimates may be averages of the penetrances of BRCA1, BRCA2, and other breast cancer–predisposing genes.

The data in this study suggest that a BRCA1-mutation carrier has a 68.6% risk of developing breast cancer by age 70 years. This estimate is similar to the value 67%, obtained from U.S. population-based breast cancer data in a study using the same controls (Claus et al. 1991); both estimates are lower than the value 85%, obtained by maximizing the LOD score over the penetrance function, and the value 87%, which was based on contralateral breast cancer occurrence in families whose LOD scores demonstrated unequivocal linkage to BRCA1 (Easton et al. 1995).

We also estimate that a woman who carries a BRCA1 mutation has a 21.5% risk of developing ovarian cancer by age 70 years. The data failed to support a model in which age-specific ovarian cancer–incidence rates in carriers are proportional to rates in noncarriers. However, the decline, with age, in the rate ratio was less steep than that seen for breast cancer, both in our data and in other data (Claus et al. 1991). The estimated

Table 5

Estimated Cumulative Risk of Breast Cancer and Ovarian Cancer, in Mutation Carriers and Noncarriers

Age (Years)	Estimated Risk (95% CI) (%)		Risk Ratio[a]
	Carriers	Noncarriers	
	Breast Cancer		
40	10.4 (4.7–21.5)	.2 (.1–.5)	42.5
50	42.3 (20.4–67.7)	1.2 (.8–1.8)	34.5
60	62.8 (31.2–86.3)	2.2 (1.5–3.2)	28.6
70	68.6 (39.5–87.9)	4.5 (3.5–5.8)	15.1
80	73.5 (47.3–89.5)	6.8 (5.4–8.6)	10.8
	Ovarian Cancer		
40	4.0 (1.1–13.3)	.1 (.0–.2)	73.9
50	9.4 (2.7–28.3)	.3 (.1–.5)	34.7
60	14.6 (3.9–41.6)	.5 (.3–.9)	29.8
70	21.5 (4.8–59.9)	1.1 (.7–1.8)	19.1
80	27.8 (5.2–73.0)	1.8 (1.1–2.8)	15.8

NOTE.—Data are based on the general dominant model; q = .0014 (95% CI .0002–.011).

[a] Risk in carriers divided by risk in noncarriers.

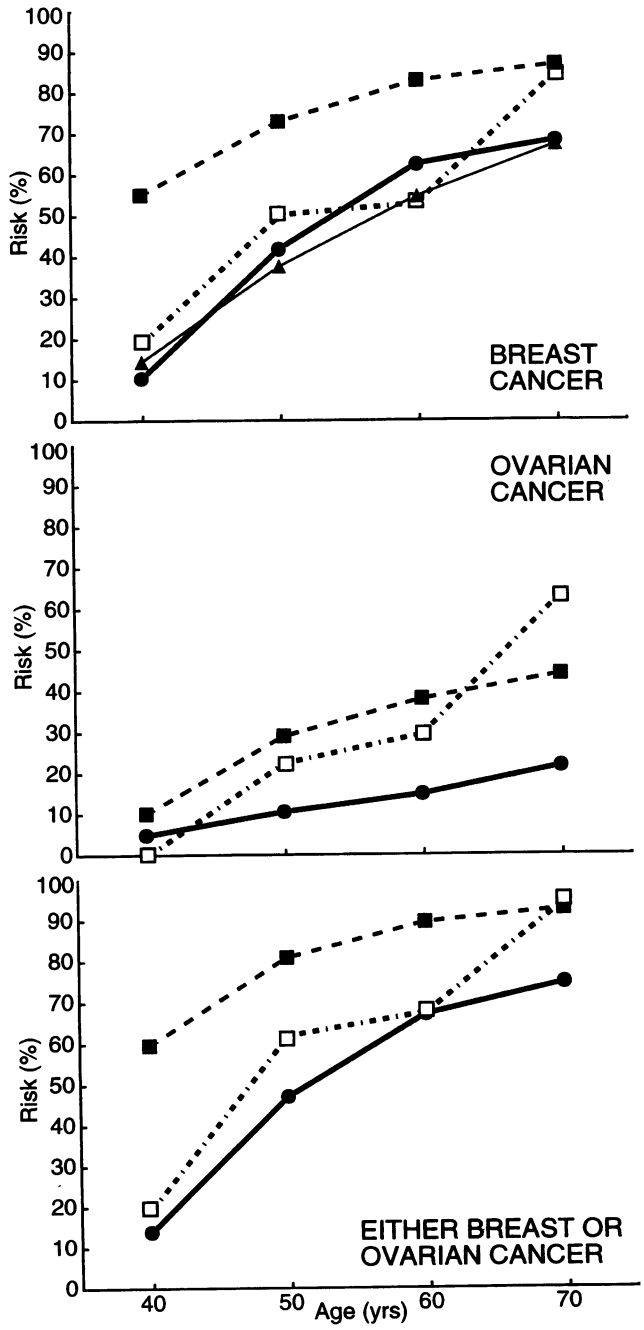

Figure 3 Estimated cumulative probability that a woman who carries a mutation of BRCA1 develops breast cancer (*top*), ovarian cancer (*middle*), or either breast cancer or ovarian cancer (*bottom*). Estimates are obtained from the following four sources: data from this study (●); data from a U.S. population-based case-control breast cancer study (▲) (Claus et al. 1991); data from families linked to BRCA1, on the basis of a second cancer occurrence (■); or the maximization of the LOD score (□) (Easton et al. 1995).

Table 6

Proportion of Cancers Due to BRCA1/BRCA2 Mutations, Estimated from Population-Based Studies

Age at Diagnosis (Years)	Proportion (95% CI) of Cancers Due to BRCA1/BRCA2 Mutation (%)			
	Breast		Ovarian	
	Present Study	Ford et al. (1995)	Present Study	Ford et al. (1995)
15–29	11.2 (1.5–51.1)	7.5	17.8 (7.9–35.4)	5.9
30–39	10.7 (1.4–49.9)	5.1	17.5 (7.7–35.2)	5.6
40–49	8.6 (1.1–43.7)	2.2	6.8 (2.7–15.8)	4.6
50–59	5.8 (.7–36.1)	1.4	6.4 (2.5–15.4)	2.6
60–69	.7 (.1–8.7)	.8	3.1 (.6–13.8)	1.8
70–79	.6 (0–7.6)	...	2.8 (.6–12.4)	...
15–69	4.2 (.6–24.7)	1.7	5.3 (2.1–12.7)	2.8
15–79	3.0 (.4–18.8)	...	4.4 (1.6–11.9)	...

21.5% risk of ovarian cancer among carriers is half the 44% estimate obtained from ovarian cancer incidence among women with a prior breast cancer in the BRCA1-linked families (Easton et al. 1995). Since virtually all the high-risk families in the present study included at least one woman with ovarian cancer, it is unlikely that the lower ovarian cancer risk estimate reported here is due to the presence of families segregating other breast cancer–susceptibility genes with low ovarian cancer penetrance. Rather, it seems more plausible that the present risk estimates are lower than those reported by Easton et al. because the latter analysis was based on families who were selected only if they demonstrated linkage to BRCA1 and whose cancer experience thus may overestimate the risks of carriers in the general population. It should be noted, however, that a heterogeneity analysis of the linkage families, by Easton et al. (1995), suggests that most BRCA1 mutations confer an ovarian cancer risk substantially lower than the 44% estimated with the assumption that all mutations confer equal risk. The present lower risk estimates and their implications for decisions on prophylactic surgeries should be useful to counselors of women in families linked to BRCA1.

The present estimates of the proportions of breast cancer and ovarian cancer due to BRCA1 in the general population are low. We estimate that only 4.2% of all breast cancers and 5.3% of all ovarian cancers diagnosed by age 70 years are due to BRCA1. Among young women (<40 years of age at diagnosis) with breast cancer or ovarian cancer, the proportions are ~11% and ~18%, respectively. These estimates are larger than those obtained from the population-based British data (Ford et al. 1995). The 11% estimate for breast cancer also is larger than the carrier prevalence noted by Langston et al. (1996) in the molecular analysis of a population-based sample of young breast cancer cases. These authors found that 6 (7.5%) of 80 women diagnosed with breast cancer by age 40 years carried germ-line mutations of BRCA1. However, this estimate may be low because of sensitivity limitations on the assay and because an additional 4 (5.0%) of the 80 women had unusual BRCA1 alleles of unknown significance.

Nevertheless, the evidence suggests that in only a small minority of young women with breast cancer or ovarian cancer is the cancer due to BRCA1. Moreover, recent data suggest a small role, in breast cancer, of mutations in BRCA2, a gene that segregates in some families with male breast cancer but with little or no ovarian cancer (Phelan et al. 1996). A substantial portion of the remaining cancers may be due to more common but less penetrant alleles of other genes (e.g., HRAS1; Krontiris et al. 1993) or to gene-gene interactions. Further work is needed, to examine this issue.

Both prior analysis of the largest of the three case-control studies (Schildkraut and Thompson 1988) described herein and recent analysis of data from Finland (Auranen et al. 1996) have suggested that breast cancer risk and ovarian cancer risk among relatives of women with borderline cancers may not be greater than that in the general population. However, the present study failed to distinguish the general dominant model from the nongenetic model as a possible explanation for the cancer occurrence in the families of probands with borderline ovarian cancer, on the basis of data from 169 such probands. In the families of non-White and Hispanic probands, there appeared to be more cancer clustering at young ages than was predicted by either the nongenetic model or the general dominant model. Such clustering, if not due to chance, might reflect a higher mutation prevalence in these ethnic groups than among non-Hispanic White women.

In conclusion, the present estimates that BRCA1 mutations account for 3.0% of all U.S. breast cancers and

for 4.4% of all U.S. ovarian cancers are in need of confirmation from other large, population-based studies, particularly multiethnic studies. There also is a need for laboratory-based estimates—of the frequencies and penetrances of specific mutations—obtained from population-based samples of women with breast cancer or ovarian cancer.

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